Therapie mit Ketoconazol bei Chorioretinopathia Centralis Serosa : eine Pilotstudie

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Meiner großartigen Mutter in besonderer Dankbarkeit gewidmet

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Abkürzungen

- CCS Chorioretinopathia Centralis Serosa
- RPE Retinales Pigmentepithel
- FLA Fluoreszein Angiographie
- OCT Optische Kohärenz Tomographie

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Zusammenfassung:

Die Pathogenese der Chorioretinopathia Centralis Serosa (CCS) ist noch weitgehend unbekannt. Vermutlich liegt dieser Erkrankung eine Dysfunktion des retinalen Pigmentepithels (RPE) und/oder der Choroidea (Aderhaut) vor, die zu einer Ansammlung von extrazellulärer Flüssigkeit in den subretinalen bzw. den Raum unter dem RPE führt. Somit ist die CCS durch eine seröse Abhebung der neurosensorischen Netzhaut und/oder des RPE charakterisiert.

Sie betrifft junge Menschen und Erwachsene mittleren Alters, Männer zu Frauen im Verhältnis 4:1. Hauptsymptome sind meist einseitiges Verschwommensehen, Metamorphopsien, Mikropsie, ein relatives Skotom und eine Farbentsättigung.

Die CCS wird in eine akute und eine chronische Form eingeteilt. Die akute Form kommt vorwiegend bei jüngeren Patienten vor und zeigt typische Veränderungen beginnend mit einem fokalen Quellpunkt mit darauf folgender Ansammlung extrazellulärer Flüssigkeit in den subretinalen Raum bzw. den sub-RPE-Raum. Die chronische Form ist durch ausgedehnte Veränderungen des RPE, verursacht durch eine chronische Ansammlung von subretinaler Flüssigkeit, gekennzeichnet.

Der Verlauf der chronischen Form ist meist progredient und die Visusprognose ist schlechter als bei der akuten Form.

Bekannte Risikofaktoren sind männliches Geschlecht, Stress, Typ A Persönlichkeit, Schwangerschaft, Hypertonie, erhöhte Catecholaminwerte, genetische Disposition, Psychopharmaka, Diabetes mellitus, frühere Augenoperationen, Antibiotika, Alkohol und Antihistaminika. Seit kurzem weiß man aber auch, dass eine erhöhte endogene Glucocorticoidproduktion und exogene Glucocorticoidtherapie bei der Entstehung der

CCS eine Rolle spielen: Corticosteroide können einerseits verschiedene Veränderungen im Bereich der Choriokapillaris verursachen und andererseits zu einem Schaden des RPE führen.

Die Chorikapillarisdurchblutung wird möglicherweise durch die parasympatholytische Wirkung der Glucocorticoide über eine Hemmung der Stickstoffmonoxid (NO)-Synthese verursacht, welche eine wichtige Rolle bei der Gefäßregulation spielt. Diese catecholaminvermittelte Vasokonstriktion choroidaler Gefäße verändert wiederum die Permeabilität bzw. die Perfusion dieser Gefäße. Glucocorticoide begünstigen aber auch die Blutgerinnung, was zu einer choroidalen Hypoperfusion führen kann. Diese Befunde würden die Hypothese, dass die Veränderung der choroidalen Perfusion eine Rolle in der Pathogenese der CCS spielt, bestätigen.

Auf der anderen Seite induzieren Glucocorticoide eine vermehrte Brüchigkeit und Hyperpermeabilität der Kapillaren, was zur direkten Leckage der Flüssigkeit in den subretinalen Raum führt. Auch die Bruch-Membran scheint von Glucocorticoiden beeinflusst zu werden, was die Anordnung der Kollagenformation, der Hauptkomponente der extrazellulären Matrix der Bruch-Membran, verhindert.

Im Bereich des RPE ist eine direkte, lokalisierte Schädigung des retinalen Pigmentepithels und ihrer tight junctions durch Glucocorticoide postuliert worden.

Zudem wird vermutet, dass Glucocorticoide im RPE auch eine Veränderung des Wasser- und Ionen-Transports verursachen.

Ketoconazol, ein Antimykotikum der Imidazole, hemmt die endogene Cortisolsynthese und wird in der Endokrinologie unter anderem therapeutisch bei Morbus Cushing eingesetzt. Eine Senkung der endogenen Cortisolsynthese durch Ketoconazol erschien daher ein innovativer und nahe liegender Therapieansatz bei Chorioretinopathia Centralis Serosa.

Ziel dieser Studie war es, einen möglichen Effekt von Ketoconazol bezüglich Visusänderung und Netzhautdickenänderung bei Patienten mit CCS zu untersuchen.

In einem Zeitraum von 19 Monaten wurden 30 Patienten der Universitäts-Augenklinik Bonn mit einer akuten CCS in diese Studie eingeschlossen. Von 30 Patienten wurden 15 aufeinander folgende Patienten 4 Wochen lang mit Ketoconazol 200mg/d behandelt, 15 weitere Patienten dienten als Kontrollgruppe. Das mittlere Alter betrug 46±10 Jahre

in der Therapiegruppe und 46±15 Jahre in der Kontrollgruppe. Das Verhältnis weiblich zu männlich betrug 1:4 in der Therapiegruppe und 1:3 in der Kontrollgruppe.
Die Diagnose der CCS wurde vor Eintritt in die Studie klinisch und durch eine Fluoreszein Angiographie (FLA) gesichert. Vor und 4 Wochen nach Therapie wurde der Visus erhoben und die Abhebung der Neuroretina bzw. des RPE mittels Optischer Kohärenz Tomographie (OCT) vermessen.
Der mittlere Visus betrug anfangs in der Behandlungsgruppe in Snellen Einheiten 0.6±0.2 (Log MAR 0.2±0.7) und in der Kontrollgruppe 0.7±0.3 (Log MAR 0.2±0.5). Im OCT betrug die mittlere Abhebung der Neuroretina bzw. des Pigmentepithels 288±163µm in der Behandlungsgruppe und 225±51µm in der Kontrollgruppe. Vier Wochen später stieg der Visus in der Therapiegruppe auf 0.7±0.2 (Log MAR 0.2±0.7) und in der Kontrollgruppe auf 0.8±0.3 (Log MAR 0.1±0.5) an, die Abhebung der Neuroretina bzw. des Pigmentepithels nahm in der Therapiegruppe auf 160±103µm und in der Kontrollgruppe auf 120±93µm ab. Die Unterschiede in den Änderungen bezüglich Visus und OCT zwischen beiden Gruppen waren jedoch statistisch nicht signifikant.

Das Ausbleiben eines statistisch signifikanten Therapieerfolges trotz rational begründetem Therapieansatz kann mehrere Ursachen haben: 1. die Anzahl der in diese Studie eingeschlossenen Patienten war zu gering, 2. die Konzentration des Ketoconazol (200mg/d) war möglicherweise nicht hoch genug. In dieser Studie wurde die zugelassene handelübliche Dosis verwendet.
Es ist aber bekannt, dass bei der Behandlung des Morbus Cushing Konzentrationen bis zu 1200mg/d Ketoconazol verordnet werden, die jedoch mit erheblich höheren Nebenwirkungen behaftet sind.
Weitere, ergänzende Studien mit einer höheren Anzahl an Patienten und/oder höherer Dosierung von Ketoconazol erscheinen deshalb sinnvoll.

Ketoconazole in the treatment of Central Serous Chorioretinopathy: A pilot study

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Abstract

Purpose: The aim of this study is to evaluate a possible effect of systemic Ketoconazole on visual acuity (VA) and retinal thickness in patients with acute central serous chorioretinopathy (CSCR).

Materials and Methods: 15 consecutive patients were treated with Ketoconazole 200 mg/d over a period of 4 weeks, while the other 15 patients served as control group. Baseline examination and review after 4 weeks included VA testing and measurement of neuroretinal or pigment epithelial detachment by optical coherence tomography (OCT). Fluorescein angiography was performed to verify the diagnosis.

Results: At baseline, mean VA in Snellen units was 0.6±0.2 (Log MAR 0.2±0.7) in the treatment group and 0.7±0.3 (Log MAR 0.2±0.5) in the control group. On OCT, mean neuroretinal or pigment epithelial detachment measured 288±163 µm in the Ketoconazole group and 225±51 µm in the control group, respectively. Four weeks later, mean VA improved in both groups. On OCT, neuroretinal or pigment epithelial detachment decreased also in the treatment group and the control group. The differences were statistically not significant.

Conclusion: While a pharmacological decrease in endogenous cortisol synthesis appears to be a rational approach in the treatment of CSCR, systemic Ketoconazole at 200mg/d was not associated with a significantly better outcome in this preliminary study.

Key words

Central serous chorioretinopathy, CSC, CSCR, corticosteroids, Ketoconazole

Introduction

The pathogenesis of central serous chorioretinopathy (CSCR) is still poorly understood. Deterioration of the outer blood retinal barrier is thought to result from a primary damage either at the level of the choriocapillaris or the retinal pigment epithelium (RPE). Changes in choroidal perfusion and choroidal permeability with focal ischemia, localized capillary and venous congestion have been proposed (Bouzas et al. 2002; Carvalho-Recchia et al. 2002; Kapetanios et al. 1998; Prunte & Flammer 1996).
A localized impairment of metabolic transport functions of the RPE leading to a reversal of the direction of ion secretion has also been suggested (Spitznas 1986). The common final pathway results in an accumulation of extracellular fluid in the subretinal and/or sub-RPE space.
CSCR is a disease characterized by serous detachment of the neurosensory retina secondary to one or more focal lesions of the RPE. It afflicts young and middle-aged adults and concerns more men than women. Symptoms are blurring of vision usually unilateral, metamorphopsia, micropsia, relative scotoma and colour desaturation (Bennett 1955; Gass 1967; Wang et al. 2008). It is subdivided into an acute and a chronic type. The acute CSCR appears predominantly in young people and shows characteristic changes starting with a focal point and resulting in an accumulation of extracellular fluid in the subretinal and/or sub-RPE space. The chronic type is characterized by more extensive RPE changes caused by a chronic accumulation of subretinal fluid. It is in the majority of cases progressive and the prognosis of visual acuity (VA) is worse than in the acute type (Spaide et al. 1996; Spaide et al. 1996).

Various risk factors for CSCR have been identified including male gender, stress, type A personality, pregnancy, arterial hypertension, elevated catecholamines, genetic disposition, psychopharmacologic medication, diabetes mellitus, previous eye surgery, antibiotics, alcohol, and antihistamines (Bouzas et al. 2002; Dohrmann et al. 2001; Gelber & Schatz 1987; Haimovici et al. 2004; Tittl et al. 1999; Wynn 2001; Yannuzi 1987).

Recently, elevated endogenous glucocorticoid production as seen in Cushing's disease or steroid-producing tumors has been shown to induce CSCR (Bouzas et al. 1993; Bouzas et al. 2002; Harada & Harada 1985; Thoelen et al. 2000).
Moreover, exogenous glucocorticoid administration in various medical conditions including asthma and other inflammatory diseases can trigger central serous chorioretinopathy (Bouzas et al. 1999; Bouzas et al. 2002; Carvalho-Recchia et al. 2002; Conrad et al. 2000; Dohrmann et al. 2001; Garg et al. 1997; Haimovici et al. 1997; Haimovici et al. 2003; Haimovici et al. 2004; Kapetanios et al. 1998; Lin & Tsai 2001; Polak et al. 1995; Tittl et al. 1999; Wakakura et al. 1997).

Ketoconazole, an imidazole derivative, is approved for the treatment of mycosis.
It is an antifungal agent that binds to fungal cytochrome P450 enzymes and destroys the cytoplasmic membrane and inhibits critical enzymes of yeast and other fungal infectious agents. It also inhibits the endogenous cortisol synthesis by blocking the formation of pregnenolone, a precursor molecule of cortisol, and the direct cortisol synthesis from 11ß-deoxycortisol (Figure 1). Due to this effect, Ketoconazole has recently been established in the treatment of Cushing's disease (Chou & Lin 2000; Winquist et al. 1995).
Patients suffering from acute CSCR are usually young and active persons who are strongly disturbed by the occurrence of the symptoms. Many of them require a sick certificate for 3-4 weeks. A therapeutic intervention that would countermand the symptoms earlier than the natural course would be very helpful not only for the well-being of the patient, but also economically.
Given the implication of corticosteroids in the pathogenesis of CSCR, Jampol,et al. (2002) proposed that the lowering of endogenous cortisol production by pharmacological intervention would be a rational approach for the treatment of CSCR (Jampol et al. 2002).
Therefore, the aim of this study is to evaluate a potential therapeutic effect of Ketoconazole in patients with acute CSCR.

Materials and Methods

Thirty consecutive patients, who were referred to our department with CSCR in a period of 19 months, were included in the study. Eligible were patients with an acute manifestation of CSCR that is characterized by serous retinal detachment, retinal pigment epithelial detachment or dysfunction without other possible cause of the exudation, such as inflammation, infiltration, or choroidal neovascularization (Haimovici et al. 2003; Tittl et al. 1999). Both new and recurrent diseases of acute CSCR were eligible. CSCR was verified by fluorescein angiography. The neurosensory or RPE detachment was additionally evaluated by optical coherence tomography (OCT).

Excluded were patients (a) with acute or chronic liver diseases (Ketoconazole increases liver enzymes); (b) women during their pregnancy and lactation period, and women of childbearing age without contraceptive protection; (c) patients taking drugs with a cytochrome-dependent metabolism such as Terfenadine, Cisaprid, Midazolam, Triazolam, Lovastarin, oral anticoagulatives, Digoxin, Ciclosporine and Methyl-prednisolone; (d) patients taking Nifedipine and Chinidine due to the intensification of their antihypertensive effect by Ketoconazole; (e) patients taking Rifampicine and Isoniazid because these drugs provoke a decrease blood levels of Ketoconazole, and (f) patients taking antacid medications and H_2 blockers because of a reduced Ketoconazole resorption.

The study was conducted as a retrospective study with concurrent control group according to the *Ophthalmology*`s study design scheme by Don Minckler (Minckler 1999).

In accordance with the institutional review board of the University of Bonn we treated 15 patients on the basis of a treatment attempt with Ketoconazole 200mg/d. Informed consent was obtained from all patients for this off-label therapy as well as for a possible later data analysis. The results of these treatments were retrospectively analyzed against those of 15 consecutive patients who hadn't received any treatment for CSCR.

Baseline examination and follow up visits 4 weeks after the onset of treatment included testing of best corrected visual acuity (BCVA) and evaluation of the amount of the

neurosensory or RPE detachment, measured by optical coherence tomography (OCT1, Zeiss Humphrey Instruments, Dublin, CA, USA). The latter was determined by placing the callipers manually, using the scan with the highest detachment. If there was an overlap of neurosensory and RPE detachment on the OCT, the heights of both detachments were added, otherwise the highest detachment was chosen for measurement. A standard protocol using radial lines with a scan length of 5.92 mm was applied. In patients whom neuroretinal and RPE detachment was present at the same time, the larger detachment was chosen for measurement and follow-up (Figure 2).

All patients were examined with dilated pupils (tropicamide- Mydriaticum Stulln UD, 92551 Stulln, Germany).

Fluorescein angiography (Zeiss FF450, Visupac) was performed to verify the diagnosis (Figure 3).

Statistical analysis was done using Wilcoxon Signed Rank Test.

Results

Average age of all patients was 46±10 years (range 30-74 years) in the treatment group, and 46±15 years (range 29-82 years) in the control group (p = 0.95). The ratio of female to male was 1:4 in the Ketoconazole group and 1:3 in the control group.

At baseline, mean visual acuity was 0.6± 0.2 (Log MAR 0.2±0.7) in the treatment group, and 0.7± 0.3 (Log MAR 0.2±0.5) in the control group. The differences were not statistically significant (P= 0.09).

Four weeks later, mean visual acuity improved to 0.7±0.2 (Log MAR 0.2±0.7) in the treatment group and to 0.8±0.3 (Log MAR 0.1±0.5) in the control group. This improvement did not represent a statistically significant difference (P=0.47) (Figure 4).

In the Ketoconazole group (8 right eyes, 7 left eyes), 12 patients presented with neurosensory detachment and 3 patients showed both neurosensory and RPE detachment.

The duration of symptoms was reported to be between 2 days and 6 weeks; 6 patients experienced their first episode of the disease, 9 patients suffered from recurrences of

CSCR. On fluorescein angiography, 10 patients displayed multifocal, and 5 patients displayed focal leakage of CSCR.

In the control group (8 right eyes, 7 left eyes), 13 patients had pure neurosensory detachment, one displayed RPE detachment, and one showed both neurosensory and RPE detachment. The duration of symptoms lasted between 1 and 6 weeks; 12 patients experienced their first episode of the disease, 3 patients had recurrences of CSCR. On fluorescein angiography, 5 patients showed multifocal, and 10 patients showed focal leakage of CSCR. The disease was only active in one eye in all patients.

Average neuroretinal and/or pigment epithelial detachment at baseline was 288 µm±163 µm in the Ketoconazole group and 225±51 µm in the control group. The differences at baseline were statistically significant (P=0.009). On average, mean neuroretinal and/or RPE detachment decreased to 160±103 µm in the treatment group and to 120±93 µm in the control group at the 4 week review, whereby the extent of reduction was not significantly different (P=0.71) (Figure 5).

During the review period, none of the patients experienced deterioration in VA or progression of the RPE/neurosensory detachment in both groups.

Only few systemic adverse effects of Ketoconazole were observed. One patient discontinued Ketoconazole after 3 weeks because of erectile dysfunction. Another one stopped taking the medication after 2 weeks because of nausea.

Discussion

Both elevated endogenous glucocorticoid production and exogenous glucocorticoid supply as oral, intravenous, intramuscular, inhaled, intranasal, intraarticular, epidural (Abu el-Asrar AM 1997; Bouzas et al. 2002; Haimovici et al. 1997; Haimovici et al. 2003; Kapetanios et al. 1998; Lin & Tsai 2001; Polak et al. 1995; Tittl et al. 1999), periocular (Baumal et al. 2004) or epidermal application (Karadimas et al. 2004) have been reported to induce CSCR.

Tittl et al. (1999) reported a retrospective case-control study of 230 consecutive patients with CSCR in comparison with a gender-matched and age-matched historical control

group. Patients with CSCR used corticosteroids and psychopharmacologic medications significantly more often, and were more likely to have a history of systemic hypertension. Carvalho-Recchia et al. (2002) investigated 50 patients with acute symptoms and clinical manifestation of CSCR and found 52% of them to have a history of exogenous steroid use. They also found two additional patients with a history of endogenous hypercortisolism. In comparison, the matched control group revealed a history of steroid use in only 18%.

Haimovici et al. (2003) tested patients with acute CSCR for elevated 24h urine cortisol or tetrahydroaldosterone levels, and found increased levels in 50% of cases.

It has been speculated that the steroid-effect on the development of CSCR may be related to the modulation of the choroidal circulation, which is regulated by the vegetative nervous system (Carvalho-Recchia et al. 2002).

Steroids act synergistically with the sympathetic nervous system and antagonize the effect of the parasympathetic nervous system. The latter is known to inhibit the production of nitric oxide (NO) synthase, an important vascular modulator. The inhibition of NO synthase leads to a catecholamine mediated vasoconstriction of the choroidal vessels, which in turn alters the permeability and/or perfusion of these vessels (Bouzas et al. 1999; Bouzas et al. 2002; Bujarborua 2001; Carvalho-Recchia et al. 2002; Deussen et al. 1993; Fernandez et al. 2004; Haimovici et al. 2003; Kapetanios et al. 1998; Mann et al. 1995; Michael et al. 2003; Spraul et al. 1997; Taban et al. 2004; Worrall et al. 1996).

Glucocorticoids also appear to promote blood coagulation, which could lead to choroidal hypoperfusion (Ozsoylu et al. 1962). These findings would support the hypothesis that alterations in choroidal perfusion may play a role in the pathogenesis of CSCR.

On the other hand corticosteroids have also been shown to induce increased capillary fragility and hyperpermeability leading to leakage of fluid in the subretinal space (Bouzas et al. 2002; Bujarborua 2001; Spraul et al. 1997; Taban et al. 2004; Gill 1990).

Bruch's membrane composition may also be influenced by cortisone, which has been shown to inhibit the formation of collagen, i.e. a major component of Bruch's membrane extracellular matrix (Oikarinen et al. 1986).

With regard to the role of the RPE, cortisol could generate alterations in the ions- and H_2O-transport due to mineralocorticoid receptors on the RPE (Bouzas et al. 2002). Furthermore, a direct damage of glucocorticoids on the RPE cells and their tight junctions has been postulated (Smith 1984).

Both findings would underscore a potential localized impairment of RPE functions as cause for CSCR.

Based on the current knowledge, potential pharmacological targets in CSCR could include agents to decrease the production of NO synthase, block catecholamine alpha- and ß-receptors, or inhibit systemic hypercortisolism (Carvalho-Recchia et al. 2002; Jampol et al. 2002).

Ketoconazole inhibits the endogenous cortisol synthesis by blocking both the formation of pregnenolone, a pre-stage cortisol, and the direct formation of cortisol from 11ß-deoxycortisol. This is why Ketoconazole is an established therapy in the treatment of Cushing's disease, whereby higher dosages up to 1200 mg/d as compared to the recommended 200 mg/d in mycosis are administered. Due to its anti-cortisol effect, Jampol et al. (2002) already hypothesized that Ketoconazole might be a candidate in the treatment of CSCR.

Meyerle et al. (2007) treated 5 patients with chronic CSCR with Ketoconazole 600mg/d for 4 weeks. Monitoring 24h urinary cortisol level showed a decrease in urinary cortisol levels. However, visual acuity, lesion height and greatest linear dimension in fluorescein angiography remained unchanged during the month of treatment indicating a lack of correlation between the determination of urinary cortisol levels and retinal outcome. In this study the sample size was very small and a control group was missing.

Our study evaluated Ketoconazole in the treatment of acute CSCR in 15 patients and compared the results to a control group. In contrast to the outcome in patients with chronic CSCR as described by Meyerle and coworkers we found an improvement in VA and a decrease in neurosensory/ RPE detachment in patients with acute CSCR after 4 weeks of treatment. However, compared to the control group, these effects were not statistically significantly different from the natural course of the disease.

The present study also has some limitations: the number of patients might not have been large enough to find statistically significant differences between the treatment and control group.
Given the fact that CSCR is a disease with a favourable natural course, a larger sample of patients may be necessary to detect significant treatment effects.
On the other hand the dosage used might not have been sufficient. The approved dosage of 200 mg/d Ketoconazole was applied in accordance with the recommendations of the manufacturer.
For the treatment of Cushing's disease, however, dosages up to 1200 mg/d have been suggested. It may be speculated that the dose used for the patients in our study was too low to achieve a statistically significant benefit. However, higher doses might also cause more side effects such as hepatoxicity, oligospermia and gynecomastia.

In conclusion, while the reduction of endogenous cortisol production appears to be a rational approach in the treatment of CSCR, this preliminary study failed to prove a therapeutic effect of 200 mg/d Ketoconazole.

Legends

Figure 1:
Ketoconazole blocks P450scc and 11ß-Hydroxylase thus leading to reduced synthesis of pregnenolone and cortisol

Figure 2:
Optical coherence tomography (OCT) demonstrating neurosensory detachment (Figure 2a/b) and complete resolution 4 weeks later (Figure 2c/d)

Figure 3:
Fluorescein angiography (same patient as in Figure 2) of a typical CSC showing focal hyperfluorescence in the early phase (Figure 3a) that enlarges smoke stag like in the later frame (Figure 3b). Figure 3c Late phase angiography demonstrates the entire area of detachment. Four weeks later (Figure 3d) only RPE atrophy remains in the area of the formerly leaking source

Figure 4:
Mean visual acuity (VA) at baseline (left) and 4 weeks later (right) in the Ketoconazole group (black column) compared to the control group (white column)

Figure 5:
Mean foveal detachment measured by OCT at baseline (left) and 4 weeks later (right) in the treatment (black column) and control group (white column)

References

Abu el-Asrar AM (1997) Central serous chorioretinopathy complicating systemic corticosteroid therapy. Eur J Ophthalmol 7:297-300

Baumal CR, Martidis A, Truong SN (2004) Central serous chorioretinopathy associated with periocular corticosteroid injection treatment for HLA-B27-associated iritis. Arch Ophthalmol 122:926-928

Bennett G (1955) Central serous retinopathy. Br J Ophthalmol 39:605-18

Bouzas EA, Karadimas P, Pournaras CJ (2002) Central Serous Chorioretinopathy and Glucocorticoids. Surv Ophthalmol 47:431-448

Bouzas EA, Philippe M, Pournaras CJ (1999) Central serous chorioretinopathy complicating solar retinopathy treated with glucocorticoids. Graefe`s Arch Clin Exp Ophthalmol 237:166-168

Bouzas EA, Scott MH, Mastorakos G, Chrousos GP, Kaiser-Kupfer MI (1993) Central serous chorioretinopathy in endogenous hypercortisolism. Arch Ophthal 111:1229-1233

Bujarborua D (2001) Long-term follow-up of idiopathic central serous chorioretinopathy without laser. Acta Ophthalmol Scand 79:417-421

Carvalho-Recchia CA, Yannuzzi LA, Negrao S, et al (2002) Corticosteroids and central serous chorioretinopathy. Ophthalmology 109:1834-1837

Chou SC; Lin JD (2000) Long-term effects of Ketoconazole in the treatment of residual or recurrent Cushing's disease. Endocr J 47(4):401-6

Conrad R, Bodeewes I, Schilling G, et al (2000) Central serous chorioretinopathy and psychological stress. Ophthalmologe 97:527-531

Deussen A, Sonntag M, Vogel R (1993) L-arginin-derived nitric oxide: a major determinant of uveal blood flow. Exp Eye Res 57:129-134

Dohrmann J, Lommatzsch A,Spital G, Pauleikhoff D (2001) Die Pathogenese der zentralserösen Chorioretinopathie. Ophthalmologe 98:1069-1073

Fernandez CF, Mendoza AJ, Arevalo JF (2004) Central serous chorioretinopathy associated with topical dermal corticosteroids. Retina 24:471-474

Garg SP, Dada T, Talwar D, et al (1997) Endogenous cortisol profile in patients with central serous chorioretinopathy. Br J Ophthalmol 81:962-964

Gass JD (1967) Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol 63:587-615

Gelber GS, Schatz H (1987) Loss of vision due to central serous chorioretinopathy following psychological stress. Am J Psychiatry 144:46-50

Gill GN (1990) The adrenal gland, in West JB: Best and Taylor´s physiological basis of medical practice. Baltimore, Williams and Wilkins ed 12:820-830

Haimovici R, Gragudas ES, Duker JS, Sjaarda RN, Eliott D (1997) Central serous chorioretinopathy associated with inhaled or intranasal corticosteroids. Ophthalmology 104:1653-1660

Haimovici R, Koh S, Gagnon DR, et al (2004) Risk factors for central serous chorioretinopathy: a case-control study. Ophthalmology 111:244-249

Haimovici R, Rumelt S, Melby J (2003) Endocrine abnormalities in patients with central serous chorioretinopathy. Ophthalmology 110:698-703

Harada T, Harada K (1985) Six cases of central serous chorioretinopathy induced by systemic corticosteroid therapy. Doc Ophthalmol 60:37-44

Jampol LM, Weinreb R, Yannuzzi L (2002) Involvement of corticosteroids and catecholamines in the pathogenesis of central serous chorioretinopathy: a rationale for new treatment strategies. Ophthalmology 109:1765-1766

Kapetanios AD, Donati G, Bouzas E, et al (1998) Serous central chorioretinopathy and endogenous hypercortisolism. Klin Monatsbl Augenheilkd 212:343-344

Karadimas P, Kapetanios A, Bouzas EA (2004) Central serous chorioretinopathy after local application of glucocorticoids for skin disorders. Arch Ophthalmol 122:784-786

Lin JM, Tsai YY (2001) Retinal pigment epithelial detachment in the fellow eye of a patient with unilateral central serous chorioretinopathy treated with steroid. Retina 21(4):377-379

Mann RM, Riva CE, Stone RA, et al. (1995) Nitric oxide and choroidal blood flow regulation. Invest Ophthalmol Vis Sci 36: 925-930

Meyerle CB, Freund KB, Bhatnagar P, et al. (2007) Ketoconazole in the treatment of chronic idiopathic central serous chorioretinopathy. Retina 27(7):943-946

Michael JC, Pak J, Pulido J, de Venecia G (2003) Central Serous Chorioretinopathy associated with administration of sympathomimetic agents.
Am J Ophthalmol 136:182-185

Minckler D (1999) Acknowledging the importance of study design in the organization and quality of manuscripts. Ophthalmology 106:11-12

Oikarinen AI, Uitto J, Oikarinen J (1986) Glucocorticoid action on connective tissue: from molecular mechanisms to clinical practice. Med Biol 64(5):221-230

Ozsoylu S, Strauss H, Diamond LK (1962) Effects of corticosteroid on coagulation of the blood. Nature 195:1214-1215

Polak BC, Baarsma GS, Snyers B (1995) Diffuse retinal pigment epitheliopathy complicating systemic corticosteroid treatment. Br J Ophthalmol 79: 922-925

Prunte C, Flammer J (1996) Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol 121:26-34.

Smith TJ (1984) Dexamethasone regulation of glycosaminoglycan synthesis in cultured human skin fibroblasts. Similar effects of glucocorticoid and thyroid hormones. J Clin Invest 74:2157-2163

Spaide RF, Campeas L, Haas A, Yannuzzi LA et al (1996) Central serous chorioretinopathy in younger and older adults. Ophthalmology 103(12):2070-9

Spaide RF, Hall L, Haas A et al (1996) Indocyanine green videoangiography of older patients with central serous chorioretinopathy. Retina 16(3):203-13

Spitznas (1986) M. Pathogenesis of central serous retinopathy: a new working hypothesis. Graefes Arch Clin Exp Ophthalmol 224:321-32

Spraul CW, Lang GE, Lang GK (1997) Central serous chorioretinopathy in systemic therapy with corticosteroids. Ophthalmologe 94:392-396

Taban Mehryar, Boyer DS, Thomas EL, Taban Mehran (2004) Chronic central serous chorioretinopathy: photodynamic therapy. Am J Ophthalmol
137:1073-1080

Thoelen AM, Bernasconi PP, Schmid C, Messmer EP (2000) Central serous chorioretinopathy associated with a carcinoma of the adrenal cortex. Retina 20:98-99
Tittl MK, Spaide RF, Wong D, Pilotto E, Yannuzzi LA, Fisher YL, Freund B, Guyer DR, Slakter JS, Sorenson JA (1999) Systemic findings associated with central serous chorioretinopathy. Am J Ophthalmol 28:63-68

Wakakura M, Song E, Ishikawa S (1997) Corticosteroid-induced central serous chorioretinopathy. Jpn J Ophthalmol 41:180-185

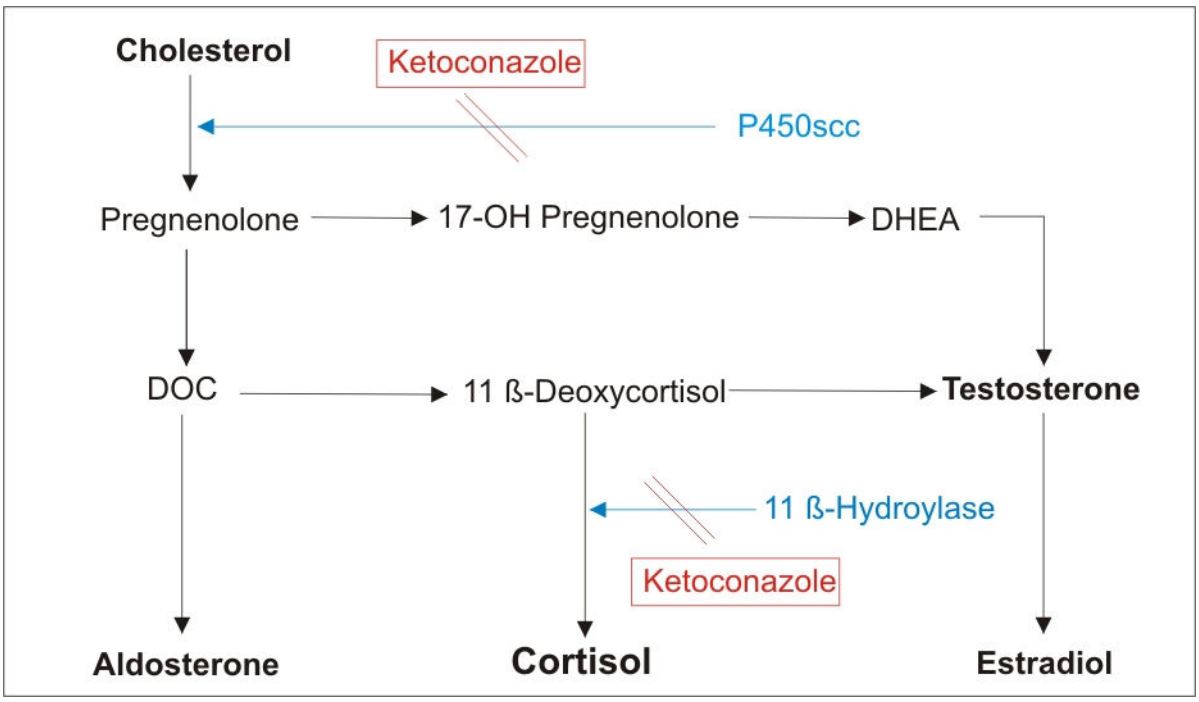
Wang M, Munch IC, Hasler PW, Prünte C, Larsen M (2008) Central serous chorioretinopathy. Acta Ophthalmol Scand 86(2):126-45. Epub 2007 Jul 28.

Winquist EW; Laskey J; Crump M; Khamsi F; Shepherd FA (1995) Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. J Clin Oncol 13(1):157-164

Worrall NK, Misko TP, Sullivan PM, Hui JJ, Rodi CP, Ferguson TB (1996) Corticosteroids inhibit expression of inducible nitric oxide synthase during acute cardiac allograft rejection. Transplantation 1996; 61:324-328

Wynn PA (2001) Idiopathic central serous chorioretinopathy_ a physical complication of Stress? Occup Med 51:139-140

Yannuzzi LA (1987) Type-A behavior and central serous chorioretinopathy. Retina 7:111-131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Ketoconazole
P450scc
Pregnenolone
17-OH Pregnenolone
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Testosterone
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Ketoconazole
Aldosterone
Cortisol
Estradiol

Figure 1

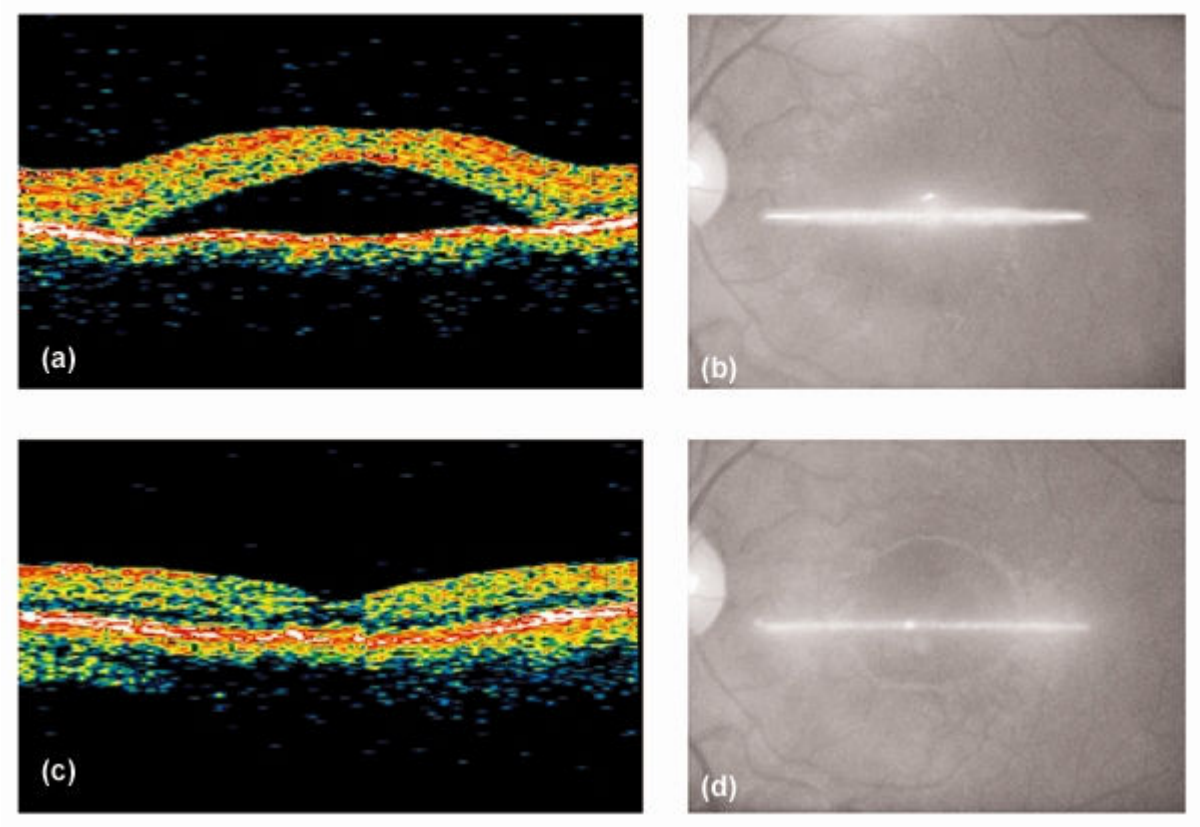


Figure 2 a, b, c, d

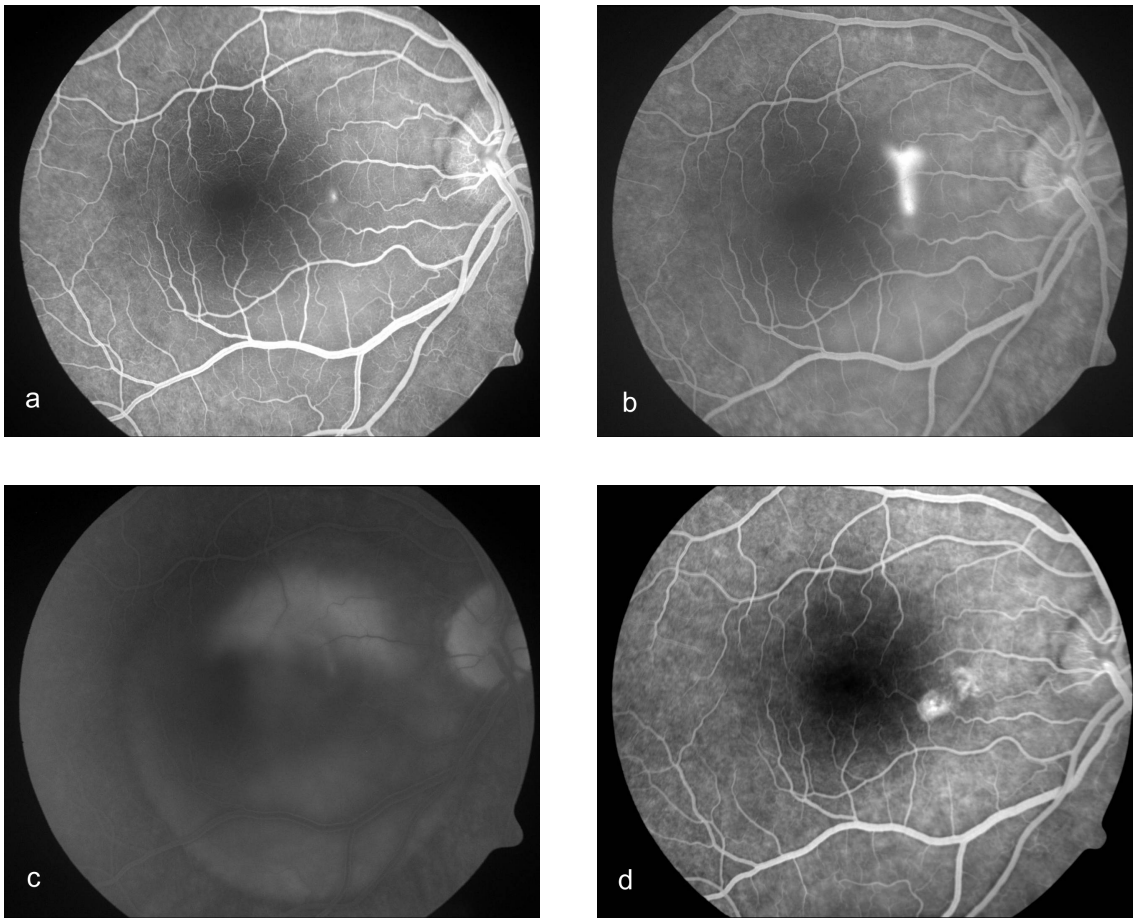
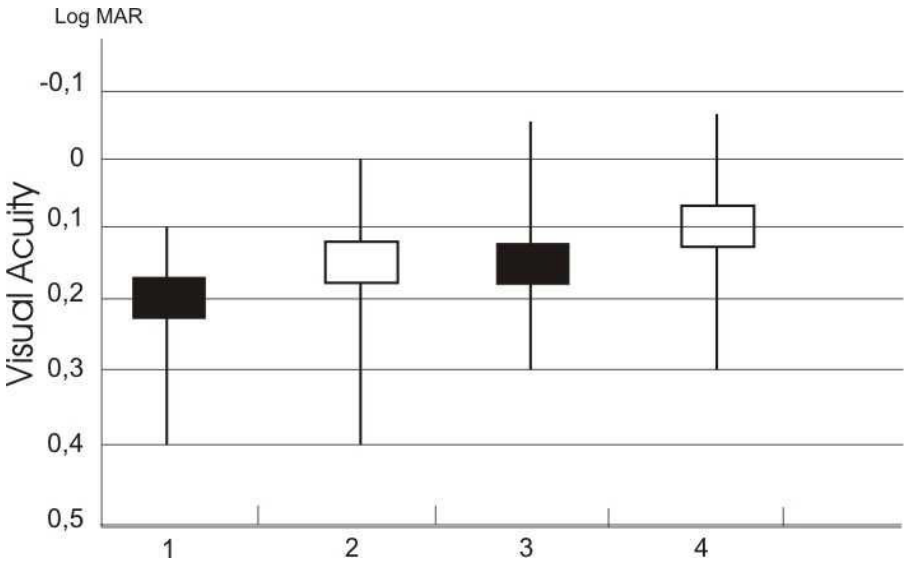


Figure 3 a, b, c, d

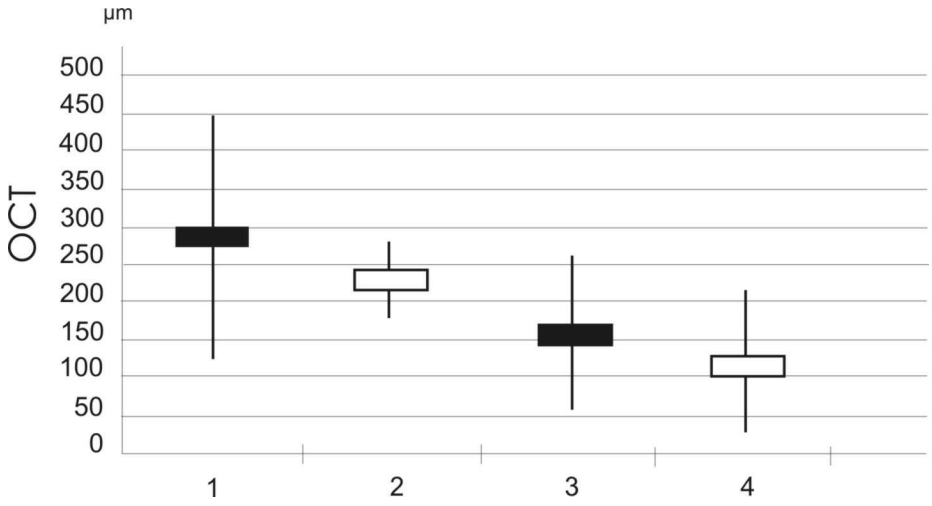


1	Baseline Therapy Group
2	Baseline Control Group
3	Follow-up Therapy Group
4	Follow-up Control Group

■	Therapy Group
□	Control Group

MEAN DIFFERENCE	
Therapy Group	**0,11**
Control Group	**0,07**

Figure 4



1	Baseline Therapy Group
2	Baseline Control Group
3	Follow-up Therapy Group
4	Follow-up Control Group

■	Therapy Group
□	Control Group

MEAN DIFFERENCE	
Therapy Group	**-127 µm**
Control Group	**-104 µm**

Figure 5

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